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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,818	BAKER ET AL.	
	Examiner	Art Unit	
	Fozia M. Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/09/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment:

1a. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09 March 2007 has been entered.

1b. Receipt of Applicant's arguments and amendment, filed on 09 March 2007 is acknowledged.

Status of Claims:

1c. Claims 28-32 are pending and under consideration.

Information Disclosure Statement:

2. The information disclosure statements submitted on 09 March 2007 has been received and complies with the provisions of 37 CFR §1.97 and §1.98. The numerous references have been placed in the application file and the relevancy of the information referred therein has been considered as best as possible.

Claim Rejections - 35 U.S.C. §101:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3a. Claims 28-32 stand rejected under 35 U.S.C. 101, for reasons of record set forth in the previous office actions mailed on 5/13/2004, 11/29/2004 and 04/03/2006.

The claims are directed to an isolated antibody that specifically binds to the polypeptide comprising the amino acid sequence set forth in SEQ ID NO:77, which is a monoclonal antibody, which is humanized, which is labeled and which is a fragment. The specification discloses that the gene encoding PRO1293 was amplified in one primary lung tumor (HF-000840) and two colon tumors, (HF:000539, and HF-000795), (see page 503, column 1). The specification asserts that gene amplification is associated with over-expression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung and other cancers, (page 494, lines 20-25). The specification also generally asserts that the polypeptides and antibodies that bind them are useful as diagnostics for cancer. However, the instant specification does not demonstrate that the PRO1293 polypeptide is actually overly expressed in any of the cancers mentioned. Applicants have not shown that there is a relationship between DNA amplification and increased amounts of corresponding mRNA or protein. Although the data in the instant specification shows that gene copy number is increased in certain tumor tissue samples, it does not necessarily follow that an increase in gene copy (DNA) number results in increased gene expression (mRNA) and increased protein expression, such that the polypeptide of SEQ ID NO:77, or antibodies that bind it, would be useful diagnostically or as target for cancer drug development. In order for PRO1293 polypeptides to be overexpressed in lung or colon tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed.

Response to Applicants' Arguments:

3b. Applicants submit, as discussed below, that not only has the PTO not established a prima facie case for lack of utility, but that antibodies claims 28-31 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed antibodies without any further experimentation. Applicants contend that the gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the claimed PRO1293 antibodies.

Initially, Applicants maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1293 polypeptides and antibodies that bind them for the reasons previously set forth in Applicants' previous responses. The Examiner respectfully maintains the position that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons previously set forth in the Office actions mailed on 3/19//2004, 11/24/2004 and 04/03/2006.

Applicants argue that the instant specification relies on the gene amplification data for patentable utility of the claimed PRO1293 antibodies, and the gene amplification data for the gene encoding the PRO1293 polypeptide is clearly disclosed in the instant specification under Example 143. Applicants argue that the gene encoding the PRO1293 polypeptide is amplified in at least three tumor samples, accordingly, Applicants contend that the present specification clearly discloses overwhelming evidence that the gene encoding the PRO1293 polypeptide is significantly amplified in

lung and colon tumors. Thus one of ordinary skill in the art would find it credible that the PRO1293 polypeptide and antibodies that bind have utility as a diagnostic marker of lung or colon tumors. Applicants submit that the Examiner asserts that the significance of the gene amplification data "can be questioned since 49 out of 52 tested tumor samples did not show an amplification of the gene encoding PRO1293".

Applicants contend that an artisan in the field of oncology would easily appreciate, that not all tumor markers are generally associated with every tumor, or even with most tumors. For example, the article by Hanna and Mornin (submitted with the Response filed September 9, 2004), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO1293 polypeptide is significantly amplified in a number of lung and colon tumors. Thus one of ordinary skill in the art would find it credible that PRO1293 has utility as a diagnostic marker of lung and colon tumors.

These arguments have been considered, but are not deemed persuasive. The fact that the gene encoding the PRO1293 polypeptide is amplified in lung or colon tumors has never been questioned. However, Applicants have not shown that the encoded polypeptide is also amplified. The issue is not the number of samples tested positive, but that there is no indication that the polypeptide is also amplified. Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Applicants could obtain patent rights to "inventions" based on a

disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in Brenner v. Manson:

> "...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

Applicants have not tested PRO1293 polypeptide expression therefore, Applicants have not been able to show that the PRO1293 polypeptide is over-expressed in these colon and lung tumors. In the absence of any information regarding PRO1293 polypeptide expression the examiner considers the asserted utilities not be specific and substantial because a skilled artisan would not know if or how PRO1293 polypeptide expression changes or antibodies that bind said polypeptide in cancer. With respect to Hanna et al. reference, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments.

Pennica et al. Pitti et al and Konopka et al.

At pages 5-10 of the response, Applicants submit that the negative control taught in the specification was known in the art at the time of filing, and accepted as a true negative control as demonstrated by use in peer reviewed publications, including

Pennica et al. and Pitti et al. (Exhibit F submitted with the Response filed 19 August 2004).

Applicants' arguments have been fully considered but they are not persuasive. Even the if the proper negative control is used, Applicants have not established if the disclosed amplification of the PRO1293 gene is one of those cases wherein the PRO1293 polypeptide is also overexpressed. Applicants have not tested PRO1293 RNA expression. Applicants have not tested PRO1293 polypeptide expression. Gene expression is, admittedly, quite complicated (Meric, page 971, right column, first paragraph of "Introduction"). Pennica suffices to show that that DNA amplification is not always associated with overexpression of the gene product.

Applicants submit that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Applicants have shown that the gene encoding PRO1293 demonstrated significant amplification, from 2.19 to 5.03 fold, in three lung and colon tumors. As explained in the Declaration of Dr. Audrey Goddard (submitted with the Response filed 19 August 2004): who considered as her scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i. e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. (Emphasis added). By referring to the 2.19-fold to 5.03-fold amplification of the PRO1293 gene in lung and colon tumors as "minor" the

Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary.

These arguments have been considered, but are not deemed persuasive. Again Applicants are missing the issue at hand. It has never been disputed that the gene encoding the PRO1293 polypeptide or antibodies that bind it are useful diagnostically. However, while the instant specification demonstrates that the PEO1293 gene is amplified in colon and lung tumors it has never shown the claimed PRO1293 is also over-expressed. Accordingly, all the arguments that pertain to how much the PRO1293 gene is overexpressed is irrelevant to the issue that the specification does not demonstrate that the PRO1293 polypeptide is overexpressed as well, so that antibodies that bind it can be used diagnostically.

Applicants have presented a number of scientific articles and expert Declarations to support their assertion that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will also be overexpressed. Applicants respectfully submit that the PTO has applied an incorrect legal standard in the instant utility rejection. Applicants contend as explained in the Appeal Brief filed 22 November 2005, the case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.

Applicants' arguments have been fully considered but they are not persuasive. Firstly, the fact to be established is, is there a Change in PRO1293 polypeptide expression in

tumors as compared the corresponding normal tissue counterpart. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of PRO1293 polypeptide expression. Nor have applicants tested PRO1293 mRNA expression. Instead, Applicants merely propose a utility that is "not implausible," relying on a general correlation between gene amplification and polypeptide expression rather than provide evidence of PRO1293 polypeptide expression. Without any evidence of PRO1293 polypeptide expression this reliance on a general correlation is of no avail to applicants because applicants have not established if the disclosed amplification of the PRO1293 gene is one of those cases wherein the PRO1293 polypeptide is overexpressed. Therefore, there is no reason for a skilled artisan to be reasonably convinced that it is more likely than not true the PRO1293 polypeptide or antibodies that bind will exhibit the asserted diagnostic behavior. In the absence of any testing of PRO1293 polypeptide expression, the specification does not provide some immediate benefit to the public for the claimed PRO1293 polypeptide or antibodies that bind. The question is not whether the diagnosis of cancer is substantial. Rather the question is whether the utility of the claimed antibodies is substantial. The specification merely invites the skilled artisan to determine if, or how, PRO1293 polypeptide expression changes so that antibodies that bind it would have utility. This utility is not substantial because further experimentation would

be required to confirm a real-world context of use. The basic quid pro quo of the patent system requires disclosure of an invention having substantial utility. Applicants' disclosure in this case does not provide a specific benefit in currently available form, and therefore lacks the substantial utility required by 35 U.S.C. § 101.

Applicants argue that the Examiner refers to the previously cited reference by Pennica et al. as "evidence that DNA amplification is not always associated with overexpression of the gene product. Applicants submit that the findings of Pennica et al. with respect to WISP-1 support Applicants' arguments. In the case of WISP-3, the authors report that there was no change in the DNA copy number, but there was a change in mRNA levels. This apparent lack of correlation between DNA and mRNA levels is not contrary to Applicants' assertion that a change in DNA copy number generally leads to a change in mRNA level. Applicants contend that they are not attempting to predict the DNA copy number based on changes in mRNA level, and have not asserted that the only means for changing the level of mRNA is to change the DNA copy number. Therefore a change in mRNA without a change in DNA copy number is not contrary to Applicants' assertions. Applicants argue that the fact that the single WISP-2 gene did not show the expected correlation of gene amplification with the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. Applicants submit that the teaching of Pennica et al. is specific to WISP genes. Pennica et al. has no teaching whatsoever about the correlation of gene amplification and protein expression in general. The test is whether it is more likely than not that gene amplification results in overexpression of the

corresponding mRNA and protein. Applicants submit that, Konopka et al. supports Applicants' position that mRNA levels correlate with protein levels. Konopka et al. states that "the 8-kb mRNA that encodes P210 $^{c\text{-}abl}$ was detected at a 10-fold higher level in SK-CML7bt-333 than in SK-CML16Bt-1 (B, +), which correlated with the relative level of P210 $^{c\ abl}$ detected in each cell line. Analysis of additional cell lines demonstrated that the level of 8-kb mRNA directly correlated with the level of P210~abl (Table 1)" (page 4050, col. 2, emphasis added). Nor does Konopka et al. support the PTO's position that DNA amplification is not correlated with mRNA or protein overexpression. Konopka et al. show only that, of the cell lines known to have increased abl protein expression, only one had amplification of the abl gene. This result proves only that increased mRNA and protein expression levels can result from causes other than gene amplification. Konopka et al. do not demonstrate that when gene amplification does occur, it does not result in increased mRNA and protein expression levels.

Applicants' arguments have been fully considered but they are not persuasive. Applicants have not established if the disclosed amplification of the PRO1293 gene is one of those cases wherein the PRO1293 polypeptide is overexpressed. Applicants have not tested PRO1293 mRNA expression. Applicants have not tested PRO1293 polypeptide expression. Gene expression is, admittedly, quite complicated (Meric, page 971, right column, first paragraph of "Introduction"). Pennica and Konopka suffice to show that that DNA amplification is not always associated with overexpression of the gene product.

Hu et al. and Chen et al references:

At pages 10-14 of the response, Applicants criticize the Hu et al. reference. Specifically, Appellant criticizes Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Applicants characterize Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Applicants criticize the types of statistical tests performed by Hu et al. Applicants argue that Hu et al. did not look for a correlation between changes in mRNA and changes in protein levels, and therefore their results are not contrary to Applicants' assertion that there is a correlation between the two. Finally, Applicants contend that they are not relying on any "biological role" that the PRO1293 polypeptide has in cancer for its asserted utility. Instead, Applicants are relying on the overexpression of PRO1293 in certain tumors compared to their normal tissue counterparts.

This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease.

However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO1293 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1293 protein can be used as a cancer diagnostic. Regarding Appellant's criticism of Hu et al.'s statistical analysis, Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicants' criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. Finally, Applicants are being asked to provide the biological role that the antibodies that bind Pro1293 polypeptide play in cancer, only to show that that the PRO1293 polypeptide is overexpressed in a lung and colon tumors as asserted.

Applicants argue that the Chen et al. reference does not support the rejection. Applicants contend that the proteins studied in the Chen et al reference were identified by staining of 2D gels. Applicants submit that it is well known that there are problems in selecting proteins detectable in 2D gels, since only relatively small and highly selected population of long-lived highly expressed proteins is observed. Thus, applicants conclude that the Chen et al authors are likely to exclude in their analysis many key regulatory proteins which could be candidate cancer markers. Applicants further

criticize the way the Chen et al authors averaged their analysis indicating that their methodology resulted in negative normalized protein values that made impossible to predict overall protein expression based on average mRNA abundance. Applicants urge that the utility standard does not require accurate prediction of protein values only that in a majority of the proteins studied it is "more likely" than not that the protein levels increased when mRNA levels increased. Applicants points out that in the Chen et al reference 40 genes out of 66 had a positive correlation between mRNA expression and protein expression, which meets the test of "more likely than not". Applicants also submit that the same authors in Chen et al (Beer et al) later published a paper reporting that oligonucleotide micrarrayss provided reliable measures of gene expression and that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma. Applicants further argue that the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels nor do the law requires that the protein levels be "accurately" predicted.

This has been fully considered but is not found to be persuasive. In the instant case, the specification provides no data showing what is the actual level of the mRNA PRO1293 in the tumor samples. There is no evidence regarding whether or not the PRO1293 polypeptide levels are also increased in these tumor samples. Since the instant claims are directed to antibodies that bind to PRO1293 polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not the overexpression of mRNA would be considered by the skilled artisan to be predictive of increased in polypeptide levels. Chen et al. was cited as providing evidence that

polypeptide levels cannot be always predicted from mRNA levels. Chen et al showed that out of 66 samples, only 9 genes were observed to show a statistically significant relationship between the protein and mRNA abundance, (see table 1 and page 309, top of column 1). This does not meet the test of "more likely than not", because the data Chen et al presented discloses that only 13.7% correlation between the mRNA expression and protein levels. The instant specification does not disclose any data regarding the level of mRNA expression (how high), therefore, one skilled in the art would not be able to predict that polypeptide level would also be increased. The Examiner is not asking that there should be a "linear" or "strong" correlation between mRNA and protein levels, but that there should be a link between the PRO1293 polypeptide and colon or lung cancer. The instant specification does not establish a link between the PRO1293 polypeptide and colon or lung cancer, all that it discloses is that the PRO1293 gene is expressed in lung and colon tumors. One skilled in the art would not be able to use the PRO1293 polypeptide or antibodies that bind in a diagnostic manner, because the specification fails to disclose whether the polypeptide is increased in these tumors as well. One skilled in the art would do further research to determine whether or not the PRO1293 polypeptide levels are increased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was

addressed in Brenner v. Manson, 148 U.S.P.Q.689 (Sup. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", '[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

With respect to the 2D gel method used by Chen et al and their data analysis, the 2D gel is a very well regarded assay for protein analysis. The Chen et al reference was published in a peer reviewed well, respected journal, therefore, the data disclosed therein is taken as being correct. Proper sample preparation is crucial for the 2D gel procedure, and there is no reason to assume that the Chen et al authors did not follow proper sample preparation. Finally, the Beer et al reference (Nature Medicine, Vol.8 (8), pages 816-824, 2002), analyzed specific genes and showed that there was a strong correlation between the oligonucleotide array data for gene expression and northern blot analysis, (see figure 2b, c). Beer et al showed that there was a strong correlation between these genes and mRNA and that mRNA levels increased from stage I and stage II adenocarcinomas and were higher than normal lung, (see page 817). This analysis was not done for PRO1293 in the instant specification. That is, it is not clear whether there was a strong correlation between the expression of PRO1293 mRNA and protein.

Haynes et al., Gygi et al and Futcher et al references:

At pages 14-17 of the response, Applicants point out that Haynes et al. never indicated that the correlation between mRNA and protein levels does not exist. Haynes et al. only state that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. Importantly, Haynes et al. did not say that for a single gene, a change in the level of mRNA transcript is not positively correlated with a change in the level of protein expression. Applicants have asserted that increasing the level of mRNA for a particular gene leads to a corresponding increase for the encoded protein. Haynes et al. did not study this issue and says absolutely nothing about it. Applicants also contend that contrary to the Examiner's statement, Haynes teaches that there was a general trend but no strong correlation between protein [expression] and transcript levels. Thus, the Haynes data meets the "more likely than not standard" and shows that a positive Correlation exists between mRNA and protein. Applicants submit that Haynes et al. may teach that protein levels cannot be "accurately predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Applicants respectfully submit that the PTO's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. Like Haynes, the Gygi reference looked at levels of mRNA at the same growth phase across different genes, not changes in mRNA levels for a single gene. Thus, when Gygi et al. state that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data," the authors are referring to correlations between constant levels of mRNA and protein at the same growth phase across different genes, not a correlation between a

change in mRNA level and a change, in protein level for the same gene and corresponding protein. Therefore, for the same reasons that Haynes is not relevant to Applicants' asserted utility, Gygi likewise offers no support for the PTO's rejection of Applicants' asserted utility.

This has been fully considered but is not found to be persuasive. Regarding Haynes et al., more than 80 polypeptides relatively homogeneous in half-life and expression level were studied, and no strong correlation between polypeptide and transcript level was found. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Specifically, Haynes et al. state, "These results suggest that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, middle of left column). Haynes et al. also state, "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general. Regarding the evidence as a whole, the PRO1293 DNA was found to be amplified in the lung and colon tumors, but the PROT1293 polypeptide was not tested to show that it also is amplified. The

requirement for such testing to reasonably confirm the asserted utility indicates that the asserted utility is not substantial, i.e., it is not in currently available form. With respect to Gygi et al, the reference teaches that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data.

Applicants submit that Futcher et al. (Mol Cell Biol. 19: 7357-68 (1999); completed a subsequent study that generated similar data, but reached different conclusions. Futcher et al. point out that "the different conclusions are also partly due to different methods of statistical analysis, and to real differences in data." In particular, Futcher et al. note that Gygi et al. used an inappropriate correlation coefficient in the analysis of their data. When the correct statistical methods were applied to the data of Gygi et al., a good correlation was seen. Futcher et al. also note that the two studies used different methods of measuring protein abundance. Futcher et al. point out that Gygi et al. may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots. In addition, Futcher et al. note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher et al. conclude that "the poor correlation of protein to mRNA for the nonabundant proteins of Gygi et al

may reflect difficulty in accurately measuring these non abundant proteins and mRNAs, rather than indicating a truly poor correlation in vivo.

Applicants' arguments have been fully considered but are not found to be persuasive. Specifically, Futcher et al. conclude that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (p. 7368, col. 1). Futcher et al. clearly emphasize that mRNA abundance might be utilized as a predictor of protein abundance only for abundant proteins. However, regarding the instant specification, one skilled in the art cannot determine if the "overexpression" of PRO1293 is statistically significant because of the lack of qualitative or numerical results. There is no guidance in the specification as to how high the levels of overexpression are. If a clinician took a colon or breast tissue sample from a patient with suspected colon or breast cancer, what is the likelihood that when compared with normal tissue, the level of PRO1293 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Applicant has provided no indication of the nature or number of samples that were used. Furthermore, in the previous Office Action, the Examiner pointed out that Futcher et al. also cites Gygi et al. who performed a similar study and generated similar data, but reaches a different conclusion (mRNA abundance is a poor predictor of protein abundance). The Examiner was unable to locate a citation in Futcher et al. indicating that the Gygi data confirm that there is a general trend between protein expression and transcript levels, as asserted by Applicant. Rather, Futcher et al.

state, "[h]owever, Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance and that 'codon bias is not a predictor of either protein or mRNA levels'" (p. 7367, col. 1, 2nd full paragraph). These two studies were only published a few months apart and clearly provide evidence as to the unpredictability in the art of predicting protein levels from mRNA levels.

Lian et al. Fessler et al. and Greenbaum et al references:

At pages 17-22 of the response, Applicants criticize the techniques used by Lian et al and conclude that these authors relied on a very insensitive measurement of the proteins studied. Applicants point out that the total number of proteins examined by Lian et al. was only 50 as compared to the approximately 7000 genes for which mRNA levels were measured. Applicants also emphasize that they are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. Finally, Applicants submit that Lian et al. only teach that protein expression may not correlate with mRNA level in differentiating myeloid cells and does not teach anything regarding lack of correlation for genes in general. Applicants contend that Fessler et al. supports Applicants' assertion that a chance in the level of mRNA for a particular protein generally leads to a corresponding chance in the level of the encoded protein. Applicants argue that instances where protein levels changed while mRNA levels were unchanged shown by Fessler et al. has no relevance to Applicants' assertion that changes in mRNA levels lead to corresponding changes in protein levels, since Applicants are not asserting that changes in mRNA levels are the only cause of

changes in protein levels. Greenbaum et al. In further support of the alleged lack of correlation between mRNA expression and protein expression levels, the Examiner cites an additional new reference by Greenbaum et al. The Examiner asserts that Greenbaum et al. reference is also not relevant to the issue at hand. Greenbaum et al. does find high levels of correlation between mRNA and protein expression in yeast cells. In particular, Greenbaum et al. reference demonstrates that a high degree of correlation is found for those genes which show a large degree of variability in mRNA expression, thus for those genes which show changes in mRNA expression, the change in mRNA expression is correlated with a change, in protein expression. In summary, Applicants respectfully submit that the Examiner has not shown that gene amplification in tumor as compared to normal tissue is not correlated with changes in mRNA and protein expression.

These arguments are not found persuasive. With respect to Lian et al. the authors concluded that there is a poor correlation between mRNA expression and protein abundance, and the fact that the total number of proteins examined by Lian et al. was only 50 as compared to the approximately 7000 genes for which mRNA levels were measured is irrelevant. Regarding Applicants' criticism of the techniques used by Lian et al asserting that the authors relied on a very insensitive measurement of the proteins studied, this reference was published in a peer reviewed well, respected journal, therefore, the data disclosed therein is taken as being correct. The Fessler et al. reference attest to the complexity of parallel comparison of genes to the corresponding mRNA transcripts and proteins. The authors note that "of interest, a poor correlation

was found between corresponding transcripts and proteins (Table VIII), as reported in other systems (31300, column 2)". Also Fessler et al show that the proteins shown on table III are known to be up-regulated by LPS and that other three proteins were up-regulated and three down-regulated with p 0.09 (page 31301, column 1). The complexity of this issue is further attested by the Greenbaum et al. reference which teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their in vivo half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Therefore, although there might be instances where the overexpression of the gene correlates well with the overexpression of the mRNA ands corresponding protein, there are many other instances where this is not true.

On pages 22-23, Applicants submit that the Examiner has not shown that gene amplification in tumor as compared to normal tissue is not correlated with changes in mRNA and protein expression. Applicants contend that the law does not require the

existence of a "necessary" correlation between gene amplification and mRNA and protein expression levels. Nor does the law require that protein levels be "accurately predicted." Applicants further contend that the data in the references cited by the Examiner confirm that there is a general trend between gene amplification and mRNA and protein expression levels, which meets the "more likely than not standard" and show that a positive correlation exists between gene amplification and mRNA and protein expression.

This have been considered, but is not found persuasive. Applicants have never been required to establish an absolute correlation between the gene amplification with changes of mRNA and protein levels for meeting the utility standard. The correlation issue is raised only because 1) it is the only basis that applicants rely upon for the asserted utility of the PRO1293 antibodies; 2) the specification merely discloses that the gene of the PRO1293 is "amplified" in lung and colon tumors, and provides no factual evidence to support for the overexpression of the polypeptide in said tumors, nor the correlation between the amplified gene and mRNA and protein levels for the PRO1293; and 3) the prior art indicates that the correlation between gene amplification, mRNA and protein may not be predictable. As addressed in detail in the previous Office Actions, the prior art also indicates that said correlation is not necessarily true in many cases, which is exemplified by the references cited by the examiner. Once again, the mere fact that there are opposing evidences in the art (references cited by applicants and references cited by the examiner, for example) is a strong indication that the correlation between mRNA and protein levels is unpredictable, not "more likely than not".

On pages 23-25, Applicants argue that they have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. Applicants have previously cited Orntoft et al., Hyman et al., and Pollack et al. as collectively teaching that in general, gene amplification increases mRNA expression. Applicants submit that the Examiner asserts that "Orntott et al. could only compare the levels of about 40 well-resolved and focused abundant proteins." (Page 18 of the Examiner's Answer). Applicants respectfully point out that Orntoft et al. found that "[i]n most cases, chromosomal gains detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%)" (page 40, col. 2; emphasis added). The level of Correlation between DNA copy number and increased mRNA levels observed by Orntoft et al., from 77-80%, clearly meets the standard of more likely than not. Orntoft et al. also found a "highly significant" correlation between mRNA and protein levels, with the two data sets studied having correlations of 39/40 (98%) and 19/26 (73%) (pages 42-43). Applicants note that while Orntofl et al. did not compare cancerous versus non-cancerous tissues, they did compare invasive versus benign tumors, thus finding genes that were markers of tumor malignancy. Applicants respectfully submit that the Examiner also appears to misunderstand the data presented by Hyman et al. The Examiner asserts that "Hyman found that up to 44% of the highly amplified transcripts were overexpressed. "Up to 44% 'does not translate into 'more likely than not'." (Page 9 of the instant Office Action).The Examiner's assessment of Hyman et al. consistent with the interpretation Hyman et al. themselves place on their data, stating that, "The results illustrate a considerable

influence of copy number on gene expression patterns." (page 6242. col. 1; emphasis added). In the more detailed discussion of their results, Hyman et al. teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (i.e., belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, col. 1; emphasis added). These details make it clear that Hyman et al. set a highly restrictive standard for considering a gene to be overexpressed; yet almost half of all highly amplified genes met even this highly restrictive standard. Therefore, the analysis performed by Hyman et al. clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression. Applicants submit that the Examiner asserts that "Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification." Applicants note that, as discussed above, the levels of amplification for PRO1293 were not "low" but significant. Thus Orntoft, Hyman and Pollack all support Applicants' position that there is more likely than not a correlation between DNA amplification and mRNA overexpression. Applicants need not demonstrate that this correlation holds 100% of the time.

Applicants' arguments have been fully considered but they are not persuasive. Omtof et al, Hyman et al and Pollack et al are evidence that at the time of applicants' invention one would not know if PRO1293 gene amplification is positively correlated with PRO1293 polypeptide expression. Applicants have not established if the disclosed amplification of the PRO1293 gene is one of those cases wherein the PRO1293 polypeptide is overexpressed. Applicants have not tested PRO1293 mRNA expression.

Gene expression is, admittedly, quite complicated (Meric, page 971, right column, first paragraph of "Introduction"). Omtoft, Hyman and Pollack suffice to show that that DNA amplifications are not always associated with overexpression of the gene product and provide evidence that one with skill in the art would not accept the alleged utility of the claimed polypeptides as obviously valid and correct. Again, Applicants are not being asked that there is correlation between DNA amplification and mRNA overexpression 100% of the time, only that the PRO1293 gene amplification leads to overexpression of the PRO1293 polypeptide as asserted by the instant specification. The Examiner never required applicants to show that DNA amplification is always associated with overexpression of the gene product. Nor did the examiner require that a polypeptide must be a known oncogene in order for amplification of the gene encoding the protein to correlate with increased protein expression. Rather, the fact to be established is, is there a change in PRO1293 polypeptide expression in tumors as compared to the corresponding normal tissue counterpart, so that the PRO1293 polypeptide and antibodies that bind would be useful diagnostically.

At pages 26-29 of the response, Applicants discuss the tow Declarations submitted by Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, which shows that, in general, there is a correlation between mRNA levels and polypeptide levels. With respect to the correlation between mRNA expression and protein expression levels, Applicants emphasize that the opinions expressed in the Polakis Declaration are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using

microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art. Applicants also discuss the second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

Applicants submit that the case law clearly establishes that the Examiner must consider all of the evidence of record anew. Applicants also draw the Examiner's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) States: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis declaration, this rejection is improper under both the case law and the Utility guidelines. Dr. Polakis' Declarations provide evidence, in the form of statements by an expert in the art that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell."

These arguments have been fully but they are not persuasive. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between a change, if any, in PRO1293 transcripts and PRO1293 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and PRO1293 polypeptide

expression the first and second Polakis declarations are of no avail to Applicants. Applicants have not provided any testing of PRO12937 mRNA expression or PRO1293 polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1293 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of PRO1293 polypeptide expression the specification does not provide some immediate benefit to the public for the PRO1293 polypeptide. None of Applicants' exhibits, arguments or declarations establish if or how expression of PRO1293 mRNA, the PRO polypeptide, or any of the other claimed polypeptides, changes in tumor tissue as compared to normal tissue. Instead, Applicants merely propose a utility that is "not implausible," relying on a general correlation between gene amplification and mRNA expression extrapolated to another general correlation between mRNA expression and protein expression without any evidence of the PRO1293 mRNA or PRO1293 polypeptide expression. Based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. See in re: Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.). Thus, the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polypeptides. The basic quid pro quo of the patent system requires disclosure of an invention having substantial

utility. Applicants' disclosure in this case does not provide a specific benefit in currently available form, and therefore lacks the substantial utility required by 35 U.S.C. § 101. Finally, the Examiner did consider both of the

Polakis' Declarations, however, Dr. Polakis does not address the issue at ahnd, that is, whether the PEO1293 gene amplification in colon and lung cancer leas to overexpression of the PRO1293 polypeptide.

On pages 28-34 of the response Applicants discuss numerous references, Alberts, Lewin, Meric, Wang, Zhigang, Manaut, Khal, Bea, among others, that allegedly support the assertion that that in general, amplification of a particular gene leads to a corresponding change in the level of expression of the mRNA and encoded protein. Applicants refer to 118 additional references as supporting their position. The teachings of these references have been acknowledged by the examiner. However, none of the cited references address the major issue in this rejection, which is whether or not the PRO1293 gene amplification in lung and colon tumor leads to overexpression of the PRO1293 polypeptide in said tumors.

Further research needs to be done to determine whether the purported increase in PRO1293 gene in lung and colon tumors supports a role for the peptide or antibodies that bind in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial.

35 U.S.C. § 112, first paragraph (Enablement):

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3c. Claims 28-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments have been fully considered but they are not persuasive. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Conclusion:

4. No claim is allowed.

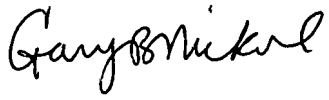
Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is 571-272-0884. The examiner can normally be reached on Monday, Thursday, Friday, 6:30-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
05 June 2007



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